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Prenatal diagnosis of HNF1B-associated renal cysts: Is there a need to differentiate intragenic variants from 17q12 microdeletion syndrome?

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Abstract: OBJECTIVE 17q12 microdeletions containing HNF1B and intragenic variants within this gene are associated with variable developmental, endocrine, and renal anomalies, often already noted prenatally as hyperechogenic/cystic kidneys. Here, we describe prenatal and postnatal phenotypes of seven individuals with HNF1B aberrations and compare their clinical and genetic data to those of previous studies. METHODS Prenatal sequencing and postnatal chromosomal microarray analysis were performed in seven individuals with renal and/or neurodevelopmental phenotypes. We evaluated HNF1B-related clinical features from 82 studies and reclassified 192 reported intragenic HNF1B variants. RESULTS In a prenatal case, we identified a novel in-frame deletion p.(Gly239del) within the HNF1B DNA-binding domain, a mutational hot spot as demonstrated by spatial clustering analysis and high computational prediction scores. The six postnatally diagnosed individuals harbored 17q12 microdeletions. Literature screening revealed variable reporting of HNF1B-associated clinical traits. Overall, both mutation groups showed a high phenotypic heterogeneity. The reclassification of all previously reported intragenic HNF1B variants provided an up-to-date overview of the mutational spectrum. CONCLUSIONS We highlight the value of prenatal HNF1B screening in renal developmental diseases. Standardized clinical reporting and systematic classification of HNF1B variants are necessary for a more accurate risk quantification of prenatal and postnatal clinical features, improving genetic counseling and prenatal decision making.

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Prenatal diagnosis of *HNF1B*-associated renal cysts: Is there a need to differentiate intragenic variants from 17q12 microdeletion syndrome?

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Abstract

Objective: 17q12 microdeletions containing *HNF1B* and intragenic variants within this gene are associated with variable developmental, endocrine, and renal anomalies, often already noted prenatally as hyperechogenic/cystic kidneys. Here, we describe prenatal and postnatal phenotypes of seven individuals with *HNF1B* aberrations and compare their clinical and genetic data to those of previous studies.

Methods: Prenatal sequencing and postnatal chromosomal microarray analysis were performed in seven individuals with renal and/or neurodevelopmental phenotypes. We evaluated *HNF1B*-related clinical features from 82 studies and reclassified 192 reported intragenic *HNF1B* variants.

Results: In a prenatal case, we identified a novel in-frame deletion p.(Gly239del) within the *HNF1B* DNA-binding domain, a mutational hot spot as demonstrated by spatial clustering analysis and high computational prediction scores. The six postnatally diagnosed individuals harbored 17q12 microdeletions. Literature screening revealed variable reporting of *HNF1B*-associated clinical traits. Overall, both mutation groups showed a high phenotypic heterogeneity. The reclassification of all previously reported intragenic *HNF1B* variants provided an up-to-date overview of the mutational spectrum.

Conclusions: We highlight the value of prenatal *HNF1B* screening in renal developmental diseases. Standardized clinical reporting and systematic classification of *HNF1B* variants are necessary for a more accurate risk quantification of prenatal and postnatal clinical features, improving genetic counseling and prenatal decision making.

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1 | INTRODUCTION

The HNF1B (hepatocyte nuclear factor-1-beta, MIM *189907; also known as transcription factor-2 [TCF2]) protein is a transcription factor that, together with its dimerization partner HNF1A, belongs to the homeodomain-containing superfamily.¹ *HNF1B* is highly expressed in numerous fetal/adult tissues, where it mediates tissue-specific gene expression, development, and function.^{2,3} It has a prominent role in fetal renal development, including regulation of organization and differentiation of renal epithelium,^{1,4,5} urogenital formation,^{4,6} and tubular development in the nephron.¹

Genetic variants affecting *HNF1B* are associated with multiple phenotypes.^{7–11} Aberrations of *HNF1B* were initially described as causative for maturity-onset diabetes of the young type 5 (MODY5; MIM #137920).^{1,8,11–13} Furthermore, *HNF1B* variants have been shown to be causal for the renal cysts and diabetes syndrome (RCAD; MIM #137920),¹⁴ renal hypodysplasia (RHD),¹⁵ familial glomerulocystic kidney disease (GCKD),¹⁶ autosomal dominant tubulointerstitial kidney disease (ADTKD, also “medullary cystic kidney disease” [MCKD] or “juvenile hyperuricemic nephropathy” [FJHN]),^{17,18} and congenital anomalies of kidney and urinary tract (CAKUT).^{8,11,15,16,19} The latter is a frequent cause of severe fetal renal anomalies often leading to termination of pregnancy (TOP), neonatal death, and chronic renal disease in children.^{19–21}

Apart from diabetes mellitus and the highly heterogeneous renal phenotype, with the most common manifestations being hyperechogenic kidneys prenatally²² and renal cysts postnatally,¹¹ *HNF1B* aberrations have been associated with several other clinical anomalies. These include agenesis or hypoplasia of the pancreas,^{8,19} impaired liver function,²³ urogenital anomalies,²⁴ electrolyte abnormalities,^{17,25} and diaphragmatic hernia.²⁶

HNF1B pathogenic variants include intragenic mutations such as single-nucleotide variants (SNVs), small insertions or deletions of bases (indels), and small copy number variants (CNVs) affecting only parts of the gene as well as larger CNVs encompassing the entire *HNF1B*.⁷ SNVs/indels described to date include nonsense, frameshift, splice-site, and missense variants. The latter are mainly distributed within exons 2 to 4, which code for the DNA-binding domain.^{8,19,22,27} All described *HNF1B* whole gene deletions so far correspond to chromosome 17q12 microdeletions spanning 1.3 to 1.8 Mb on average and including neighboring genes.^{10,28,29} Both intragenic variants and genomic rearrangements contribute almost equally to the *HNF1B*-associated phenotype.¹¹

Importantly, numerous studies reported neurodevelopmental disorders (NDDs) in individuals with 17q12 microdeletions (MIM #614527) containing *HNF1B*.^{10,28–33} Although NDDs were considered an exclusive feature of chromosome 17q12 microdeletion syndrome (17q12DS), there are recent reports also in individuals with intragenic *HNF1B* alterations.^{16,34–36}

In this study, we report on a series of seven individuals with intragenic *HNF1B* aberrations or 17q12DS and describe their renal and extra-renal phenotypes prenatally and in childhood or adult life. By comparing our

findings of this cohort with reports from current literature, we discuss the potential need to differentiate intragenic variants from 17q12DS in the increasingly common setting of prenatally diagnosed kidney abnormalities. This question is important not only for prenatal decision making but also for postnatal management in affected individuals.

2 | SUBJECTS AND METHODS

2.1 | Individual 1 (I1)

A pregnant woman presented to our Department of Obstetrics and Gynecology at gestational week 21 5/7 for sonographic examination. An isolated bilateral renal cortical hyperechogenicity without kidney enlargement was noted in the fetus. Amniotic fluid volume was normal, and amniocentesis was performed. Prenatal ultrasound at 32 weeks of gestation additionally revealed bilateral fetal pyelectasis. The female individual I1 was born at gestational week 36 6/7 with normal birth parameters. During the neonatal period, she manifested a temporary respiratory adjustment disorder and feeding problems. Postnatal kidney ultrasound at 3 months of age demonstrated a regression of renal hyperechogenicity, bilateral renal cysts of varying size, with the largest being 3 mm, an enlarged right kidney with a total volume of 24 mL (97. P), renal pelvis dilatation grade I (8 mm) of the left kidney, and bilateral megaureters of 2 mm. Sonographic examination of liver and pancreas exhibited no structural anomalies. Blood glucose level was slightly increased (110 mg/dL), indicating a predisposition to diabetes. Urine albumin/creatinine ratio was 504 mg/g. Plasma magnesium and uric acid concentrations as well as liver transaminases were normal. Additional postnatal findings included a minor atrial septal defect. Ocular anomalies were not detected. At the time of last assessment at age of 3 months, development and growth were in the normal range. Renal sonographic examination of both parents did not reveal any abnormalities (Figure 1C,D, Table 1, and Supplementary Note).

2.2 | Individuals 2 to 7 (I2–I7)

Clinical data of individuals I2 to I7 who presented with renal and/or neurodevelopmental phenotypes at our genetic outpatient clinic and at the Center for Rare Diseases Erlangen were retrospectively collected for this study (Figure 1B). Detailed clinical descriptions are provided in Table 1 and Supplementary Note. Individual I7 was previously described.³⁷

2.2.1 | Genetic analyses including sequencing and chromosomal microarray analysis

Details for next-generation sequencing (NGS)-based panel and Sanger sequencing methods as well as chromosomal microarray analysis (CMA) methods are described in Supplementary Note and Supplementary File 2. In brief, a custom panel was sequenced on an Illumina MiSeq, processed bioinformatically as described³⁸ and analyzed for variants in four genes (*PKD1*, *PKD2*, *PKHD1*, and *HNF1B*) associated with polycystic kidney disease. Sanger sequencing was used to confirm and validate the segregation of identified variants, and long-range polymerase chain

reaction (PCR) with subsequent Sanger sequencing was used to analyze the duplicated regions of *PKD1*. Chromosomal microarray analysis data were analyzed for CNVs ≥ 100 kb using Software ChAS and evaluated against control databases (Supplementary Note).³⁹

2.2.2 | Computational analyses of *HNF1B* variants

The clustering analysis of described *HNF1B* variants, the collection of these variants from the literature together with computational analyses of all possible single amino acid (AA) deletions, and missense substitutions as well as the protein structure analysis of the Gly239del variant are described in the Supplementary Note, and all data are provided in Supplementary File 1. In brief, we collected an up-to-date list of 217 intragenic *HNF1B* variants from 88 articles and public databases, harmonized these according to the HGVS nomenclature, annotated them with different computational scores, and evaluated their pathogenicity according to the American College of Medical Genetics and Genomics (ACMG) criteria. To analyze the spatial clustering, we plotted the distribution of these variants across the linear protein representation and estimated *P* values from empiric distributions of drawing the observed number of missense variants in the respective

domains. Additionally, we used the published tertiary protein structure of *HNF1B* to analyze the potential effect and proximity to other pathogenic variants of the herein identified c.715_717del, p.(Gly239del) variant.

2.2.3 | Review of reported clinical features in literature

To analyze the variable reporting of clinical symptoms in the literature, we searched all 88 above-identified publications for 12 features associated with *HNF1B* disorders. If the presence or absence of the respective feature was mentioned, we scored the publication as 1, if not as 0. Additionally, we categorized the publication type (review, case reports [less than three cases], case series [more than equal to three], and screening of *HNF1B* and/or other genes in larger cohorts), the medical specialty (according to the journal topic or first/last authors' affiliations), the *HNF1B* variant types analyzed (17q12del and/or SNV/indel), and whether the publication described born individuals or fetal cases. The detailed results of this review are represented in Supplementary File 1 (sheet "publications_reviewed") and Figure S3 and summarized in Table 2.

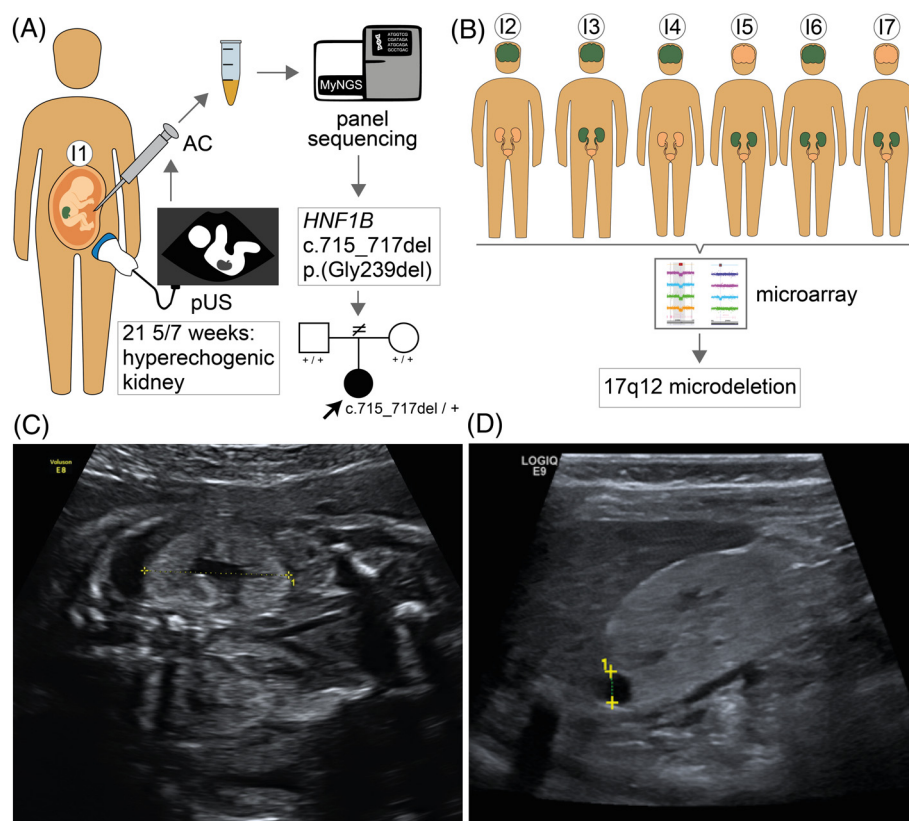


FIGURE 1 A, Pictogram describing the prenatal diagnosis of hyperechogenic kidneys in individual I1 at gestational age 21 5/7 weeks followed by amniocentesis and targeted panel sequencing, which identified the *HNF1B* variant c.715_717del. Postnatal segregation analysis in the healthy parents confirmed *de novo* occurrence of the variant (pedigree). B, Pictogram summarizing the causes for referral of individuals I2 to I7 with 17q12 microdeletions. Affected organ systems are marked in dark green: brain, neurodevelopmental disorder; kidneys, renal dysfunction; and a combination thereof both. C, Prenatal fetal sonography of individual I1 at gestational week 26 showing renal cortical hyperechogenicity with reduced corticomedullary differentiation. D, Postnatal sonography of individual I1 at 5 months of age showing multiple small and one larger cyst of the right kidney [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical and molecular findings in seven individuals with *HNF1B*-associated phenotype

	Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	Individual 6	Individual 7 ³⁷
Causes of referral	Renal anomalies	Neurodevelopmental disorder	Neurodevelopmental disorder	Neurodevelopmental disorder	Renal anomalies	Renal anomalies	Renal anomalies
Genetic change	c.715-717del, p.(Gly239del)	17q12del	17q12del	17q12del	17q12del	17q12del	17q12del
Inheritance	De novo	De novo	Mother not carrier, father not available	De novo	De novo	De novo	De novo
Diagnosis	Prenatal	Postnatal	Postnatal	Postnatal	Postnatal	Postnatal	Postnatal
Sex	Female	Male	Male	Female	Female	Female	Female
Birth parameters	Weight: 2650 g Length: 47 cm Head circ.: 33 cm Apgar: 9/9/10	Weight: 3620 g Length: 53 cm Head circ.: 36.5 cm Apgar: 10/10	Weight: 3020 g Length: 52 cm Head circ.: 32 cm Apgar: 10/10	Weight: 2730 g Length: 48 cm Head circ.: 35 cm Apgar: 10/10	NA	NA	NA
Age at latest follow-up	3 mo	8 y 8 mo	15 y 8 mo	12 y	18 y	28 y	45 y
Age at diagnosis of renal disease	Prenatal: 21 wk 5 d Postnatal: 3 mo	-	12-15 y	-	Approximately 14 y	>26 y	4 mo
Renal disease	Prenatal: hyperechogenic kidneys, pyelectasis Postnatal: bilateral renal cysts kidney enlargement renal pelvis dilatation bilateral megaureter	Prenatal: NA Postnatal: NA	Prenatal: NA Postnatal: bilateral renal cysts	Prenatal: NA Postnatal: -	Prenatal: NA Postnatal: bilateral renal cysts, stage II of chronic kidney disease	Prenatal: NA Postnatal: recurrent urinary tract infections in childhood, bilateral renal cysts, end-stage renal disease	Prenatal: NA Postnatal: right kidney agenesis, left kidney hypoplasia, recurrent interstitial nephritis, end-stage renal disease
Developmental delay/cognitive impairment	-	Learning difficulties	Mild ID	Motor delay in childhood, learning and concentration difficulties, low-normal IQ	-	Motor delay in childhood	-
Autism	-	-	Asperger syndrome	Autistic-like behavior	-	-	-
Behavioral anomalies	-	Oppositional behavior	Hyperactivity, restlessness, abnormal social behavior	-	-	-	-
Epilepsy	-	-	-	-	-	Single seizure attack in adulthood	-

(Continues)

TABLE 1 (Continued)

	Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	Individual 6	Individual 7 ³⁷
Brain anomalies	NA	-	NA	Enlarged brain ventricles	-	NA	NA
Diabetes	110 mg/dL	NA	-	-	+	+	-
Other extra-renal manifestations	Atrial septal defect	Ventricle septum defect	-	Short stature, increased hepatic enzymes Brown's syndrome	Mild strabism	Increased hepatic enzymes, biliary cirrhosis because of liver cysts	Strabism convergence, uterus aplasia, ovarian cysts, aortic insufficiency, joint hyperextension
Abnormal magnesium concentration	-	NA	-	NA	NA	NA	NA
Hyperuricemia	-	NA	NA	NA	+	NA	NA

Abbreviations: +, present; -, absent; ID, intellectual disability; IQ, intelligence quotient; NA, not analyzed.

3 | RESULTS

3.1 | Prenatal identification of a pathogenic in-frame deletion in individual I1

Prenatal panel sequencing in individual I1 revealed a novel heterozygous 3-bp deletion in exon 3 of *HNF1B* (NM_000458.3: c.715_717del), resulting in an in-frame deletion of the highly conserved AA glycine at position 239 (p.(Gly239del)) (Figure 2B). The identified indel variant was not present in the Genome Aggregation Database (gnomAD) and was computationally predicted (CADD, MutationTaster) to be deleterious. A potential splice effect was not detected (Human Splicing Finder, version 3.1). The c.715_717del variant could not be identified in DNA from peripheral blood lymphocytes of both parents and thus likely arose *de novo*. Structural modeling based on the crystal structure of the HNF1B protein showed that the glycine at position 239 (Gly239) lies in an alpha-helix motif of the homeodomain, which has DNA-binding function. The deletion of Gly is predicted to disrupt two neighboring AAs (Trp238 and Lys237) involved in binding to DNA (Figure 3). Two missense variants (c.715G>C, p.(Gly239Arg)⁴⁰; and c.716G>A, p.(Gly239Glu)⁴¹) affecting the same AA were reported in a boy with bilateral renal cysts, kidney failure, and diabetes in childhood and in a girl with MODY, renal cysts in the right kidney, agenesis of left kidney, and pancreas atrophy, respectively. Furthermore, a variant affecting the neighboring residue Trp238 (c.712T>C, p.(Trp238Arg)) was described as pathogenic (Figure 3).⁹ On the basis of the ACMG criteria⁴² (*de novo* occurrence, no inclusion in population databases, previously described variant at the same position, affected highly conserved AA, and computationally indicated pathogenicity), we classified the identified variant as pathogenic (class 5).

3.2 | 17q12 microdeletions in individuals I2 to I7

Postnatal high-resolution CMA in individuals I2 to I7 revealed 17q12 microdeletions of variable sizes ranging from 1.42 Mb in I5 to 1.80 Mb in I6 (Figure 2A). *De novo* occurrence was confirmed in all cases apart from individual I3, where the deletion was excluded in the mother, but paternal DNA was not available (see also Table 1 and Supplementary Note).

3.3 | Clinical features of the affected individuals

Prenatal renal anomalies such as hyperechogenic kidneys were only identified in individual I1 with the in-frame deletion in *HNF1B* (Figure 1C), whereas information on prenatal kidney examination of the remaining individuals was not available. Postnatally, 4/7 individuals exhibited renal cysts. Individual I1 was diagnosed with multiple renal cysts in early infancy (Figure 1D), I3 and I5 in puberty, and I6 in adulthood. Other renal abnormalities included kidney enlargement, renal pelvis dilation, and bilateral megaureter in individual I1 as well as right kidney aplasia and left kidney hypoplasia in individual I7. Recurrent urinary tract or kidney infections from childhood

TABLE 2 Reported prevalence for 12 clinical features associated with 17q12DS or *HNF1B* variants and frequency of these phenotypes as described in 82 published articles with clinical data on born individuals

Phenotype	HPO	Reported ^a	Prevalence in Literature
Abnormality of the kidney	HP: 0000077	76/82 (92.7%)	61%-91%
Neurodevelopmental delay	HP: 0012758	10/82 (12.2%)	30%-89%: 17q12 deletions 11%: <i>HNF1B</i> variants
Diabetes mellitus	HP: 0000819	76/82 (92.7%)	9%-82%
Abnormality of the genital system	HP: 0000078	39/82 (47.6%)	18%-80%
Elevated hepatic transaminase	HP: 0002910	35/82 (42.7%)	12.5%-84%
Abnormality of the liver	HP: 0410042	24/82 (29.3%)	20%-32%
Abnormality of the pancreas	HP: 0001732	33/82 (40.2%)	6%-54%
Abnormality of brain morphology	HP: 0012443	3/82 (3.7%)	4%-50%
Short stature	HP: 0004322	16/82 (19.5%)	4%
Abnormality of the eye	HP: 0000478	7/82 (8.5%)	40%-44%
Abnormal magnesium concentration	HP: 0004921	21/82 (25.6%)	25%-75%
Hyperuricemia	HP: 0002149	31/82 (37.8%)	<10-67%

Abbreviation: HPO, Human Phenotype Ontology terms.

^aFraction of publications mentioning the respective feature (eg, absence or presence count as mentioned).

onward were reported in individuals I6 and I7. Individuals I5 and I7 developed stage II and end-stage renal disease in their late teens, and I6 developed end-stage renal disease after the age of 26. In individuals I2 and I4, no renal manifestations were reported at last follow-up, at the age of 8 years 8 months and 12 years, respectively.

Two individuals had diabetes, both diagnosed in puberty (I5 and I6). I1 showed slightly increased blood glucose levels at 3 months of age. Other extra-renal manifestations included strabism (I4, I5, and I7), elevated liver enzyme levels (I4 and I6), liver cysts and primary biliary cirrhosis (I6), hyperuricemia (I5), short stature (I4), uterus aplasia and ovarian cysts (I7), and cardiac anomalies (I1, I2, and I7).

The most prominent extra-renal phenotypes in individuals with 17q12DS were NDDs and behavioral problems (Figure 1B). Individual I2 exhibited learning difficulties, I3 mild intellectual disability and Asperger syndrome, and I4 a low-normal IQ with learning and concentration difficulties. Behavioral problems varied from oppositional behavior (I2) and hyperactivity and restlessness (I3) to autistic-like behavior (I4). Motor milestones were delayed in I4 and I6. Individual I6 had a single seizure attack in adulthood. Finally, magnetic resonance imaging (MRI) showed enlarged brain ventricles in individual I4 (Table 1 and Supplementary Note).

3.4 | Reviewed intragenic variants and clustering in protein domains

We retrieved a total of 217 intragenic *HNF1B* variants from databases, 88 published articles, and this report (I1) (Supplementary File 1). Only 46/216 variants (21.3%; excluding the variant in individual I1) were deposited in public databases as of 2018-12-02. After manual review, 192 of them could be classified as ACMG class 4 (likely pathogenic; *n* = 57) or 5 (pathogenic; *n* = 135). For four variants described in the literature, there was enough evidence to classify them as

ACMG class 2 (likely benign), while for 21 variants, only insufficient information was available, and they were classified as ACMG class 3 (uncertain significance). The majority of (likely) pathogenic variants in *HNF1B* are truncating (59.4%; 114/194), whereas missense variants, clustering in important protein domains, constitute the second largest group (39.1%; 75/194) (Figure 2B and Supplementary File 1).

Besides the c.715_717del variant in individual I1, two larger indels of 30 bp (c.1118_1147del) and 75 bp (c.410_484del) are annotated as in-frame variants deleting 10 (p.(Ala373_Gln383delinsGlu)) or 25 (p.(Arg137_Lys161del)) AAs, respectively. While these two variants are annotated as “disruptive” (Figure 2B, marked in purple below protein scheme) because they ablate multiple AAs that likely disrupt the protein structure, the herein identified in-frame deletion of glycine at position 239 (p.(Gly239del)) is annotated as “conservative” (Figure 2B, marked in purple above protein scheme). Besides affecting an AA position previously described as mutated in patients with *HNF1B*-associated disease, the deletion is located within the *HNF1B* homeodomain, which mediates DNA binding.

The *HNF1B* homeodomain and the second half of the N-terminal domain (“HNF-1_N”) host the two mutational hot spots for missense variants, while likely gene disruptive variants are dispersed throughout the protein (Figure 2B, middle panel). The possible missense variants in these two domains additionally have significantly higher CADD scores when compared with those of the C-terminal domain (“HNF-1B_C”) or nondomain regions of the *HNF1B* protein (Figure 2B, lower panel; and Figure S1).

4 | DISCUSSION

Improved sonographic technologies increasingly enable the identification of fetal hyperechogenic and/or cystic kidneys. Nevertheless, identifying the underlying cause and specifying prognosis remain

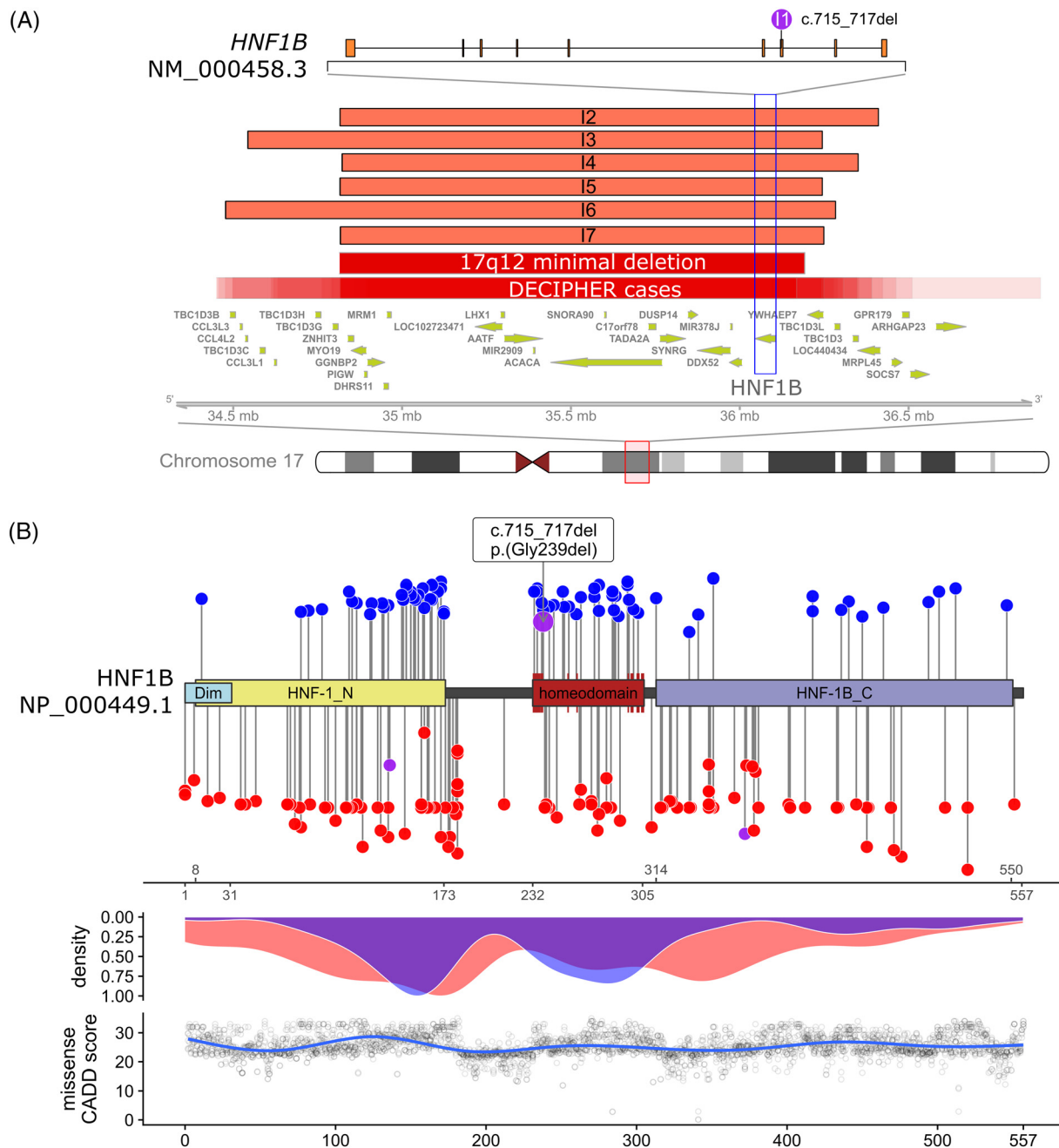


FIGURE 2 A, 17q12 microdeletions on chromosome 17q12 (red box) identified in individuals I2 to I7 (light red labeled bars) with location of genes typically affected by these copy number variants (CNVs) (see also Supplementary File 1, sheet “CNV_genes”). Dark red bars indicate the minimal 17q12 microdeletion and the variability observed in 33 cases from the DECIPHER database, respectively. The location of *HNF1B* gene within the CNV is highlighted (blue box), and the exon structure for transcript NM_000458.3 is indicated above the blue box. Location of the c.715_717del variant in exon 3 is indicated by the purple circle. B, Top panel: linear schematic representation of the *HNF1B* protein (based on NP_000449.1) with domains (limits indicated by ticks below the x-axis) and localization of all described (likely) pathogenic variants (length of the segments corresponds to the variants CADD score). The small red segments on the homeodomain represent amino acid (AA) residues directly involved in DNA binding or with specific DNA base contacts. Dim, N-terminal dimerization domain specific for the formation of homodimers or heterodimers with *HNF1A*; HNF-1_N, N-terminal domain involved in DNA binding; homeodomain, DNA-binding domain; HNF-1B_C, C-terminal transactivation domain which mediates the transcription and recruitment of coactivators.⁵⁷ The blue circles indicate all missense variants (above the schematic) and the red all truncating variants (below the schematic) described in the literature and databases. The in-frame indel c.715_717del, p.(Gly239del) (above the schematic and presented as larger circle) and two in-frame deletions of whole exons (below the schematic) are presented in purple. Middle panel: density plot of truncating (red) and missense (blue) variants reported. Missense variants show a maximal density at AA 154 in the HNF-1_N domain and a local maximum at AA 280 in the homeodomain. Bottom panel: generalized linear model of the CADD score for all possible missense variants (circles) in *HNF1B* [Colour figure can be viewed at wileyonlinelibrary.com]

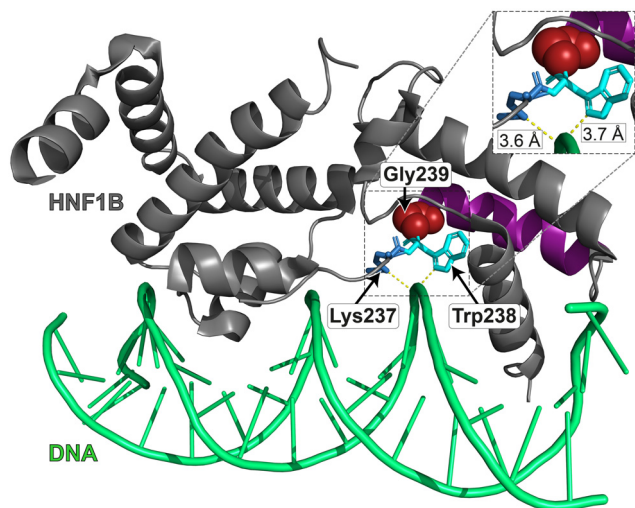


FIGURE 3 Crystal structure of *HNF1B* (grey) monomer bound to the DNA double helix (green) based on PDB 2H8R.⁵⁷ The amino acid (AA) residue Gly239 mutated in individual I1 is shown in sphere representation (red). The neighboring residues Trp238 (cyan) and Lys237 (blue) are annotated as having a “specific DNA base contact [s]” or being involved in “DNA binding,” respectively (based on NCBI NP_000449.1). Additionally, the variant c.712T>C, p.(Trp238Arg), has been reported as pathogenic.⁹ The typical alpha-helix breaker glycine at position 239 is located at the end of an alpha-helix motif (residues 240–252; purple), and its deletion (I1 described herein) or substitution^{40,41} likely disrupts the conformation and positioning of the AAs Lys237 and Trp238 required for DNA binding of the *HNF1B* transcription factor. The dashed box shows a close-up view of the affected region and the distances between the AA residues and the DNA double helix in angstrom [Colour figure can be viewed at wileyonlinelibrary.com]

challenging. The recurrent 17q12 microdeletion encompassing *HNF1B* constitutes a frequent differential diagnosis for fetal renal anomalies with variable postnatal consequences ranging from isolated renal to more complex, syndromic manifestations.^{11,15,19,22} The emerging role of *HNF1B* intragenic variants for prenatally detected renal and extra-renal phenotypes has only recently been recognized.¹¹

Panel sequencing of common genetic causes for prenatal-onset kidney anomalies in individual I1 with hyperechogenic kidneys in fetal ultrasound identified the novel in-frame single AA deletion c.715_717del, p.(Gly239del) in *HNF1B*. This is the first report of an in-frame *HNF1B* variant leading to a renal phenotype resembling that of previously described *HNF1B* cases. One of the main questions in this prenatal situation was further prognosis. Because of the variable presentation of *HNF1B* aberrations with renal and extra-renal plus possible neurodevelopmental aspects, this is particularly challenging. Currently, prenatal prognosis and decision making regarding TOP depend mainly on clinical presentation including oligohydramnios and detectable congenital anomalies. However, other issues to consider during prenatal genetic counseling without severe complications are frequency and severity of the various postnatal manifestations.

In this regard, the association of 17q12DS with a wide spectrum of NDDs in 30% to 89% individuals is of particular importance (Table 2).^{10,29–33,43} In our cohort, three individuals diagnosed with 17q12DS (I2–I4) presented primarily with psychomotor deficits and behavior anomalies, and two (I4 and I6) required therapy for delayed motor development in childhood. Although very young, individual I1 with the intragenic *HNF1B* variant did not show any signs of developmental delay. Clissold and colleagues provided evidence for association of NDDs exclusively with 17q12 microdeletions but not with *HNF1B* intragenic variants.³⁰ The predominant hypothesis for the neurodevelopmental phenotypes was haploinsufficiency of other genes encompassed by the deletion.^{28,29,31,33,43} Until recently, only single cases of NDDs in carriers of intragenic *HNF1B* variants had been reported.^{16,34,36} However, a recent study described NDDs in (6/54) 11% of individuals with MODY harboring *HNF1B* intragenic alterations; this frequency was significantly higher than in cases who had another cause of diabetes and not significantly different from 17q12DS cases (17.0%; 9/53).³⁵ This study only excluded CNVs and fragile X syndrome in individuals with NDDs without further application of exome sequencing. This leaves the possibility of a second, independent variant causing a blended phenotype, as has been shown for 4.9% of the cases in a large cohort of individuals receiving exome sequencing for different diseases.⁴⁴ After the report of NDDs in carriers of intragenic variants, *HNF1B* has been included in curated gene lists for NDDs (SysID⁴⁵; PanelApp “Intellectual disability Version 2.595”), without experimental data supporting the clinical observations. Contradicting this association, no intragenic *HNF1B* variant has been observed in several thousand individuals of large cohorts with autism⁴⁶ or developmental disorders.⁴⁷ Thus, it still remains unclear whether there is a causal link of *HNF1B* loss-of-function to NDDs. The difficulty of quantifying the NDD risk in both groups with *HNF1B* deletions and intragenic alterations is a primary cause of parental dilemma during prenatal decision making. Further complicating estimation, published patient cohorts and case reports are often limited to describing only a subset of *HNF1B*-associated clinical traits, as shown by our evaluation for 12 *HNF1B*-associated phenotypes mentioned in 82 published studies reporting phenotype data on born individuals (Table 2, Figure S3, and Supplementary File 1). New studies should follow a minimal, standardized clinical reporting scheme (Table 2) to enable fast systematic reviews and facilitate future estimation of prevalence for important symptoms like NDDs. Next to this clinical evaluation, behavioral analysis experiments of *HNF1B* knockout animal models may provide further insight of the involvement of this gene in neurodevelopment.

Postnatally, the presence of accompanying organ anomalies is important to guide appropriate management and surveillance. In the present study, 5/7 (71.4%) individuals with either *HNF1B* intragenic variant or larger deletion had renal manifestations, in agreement with the previously reported 61% to 91% prevalence in *HNF1B* cases (Table 2).^{9,48} Absence of renal disease in individuals I2 and I4 may be attributed to a milder renal phenotype overshadowed by developmental deficits³³ or to their young age. Even though renal anomalies were only prenatally reported in individual I1 in our cohort, we cannot

exclude that they were present but not detected or were not tested at all in the remaining cases with renal manifestations identified after birth (I3 and I5-I7). In the literature, the severity of prenatal renal phenotypes is not correlated with the type of *HNF1B* aberrations.¹¹ Notably, *HNF1B* intragenic variants progressively result in more severe renal function impairment and poorer renal prognosis postnatally than 17q12 deletions.^{9,30} Accordingly, renal cysts were diagnosed in individual I1 directly after birth, whereas 4/6 (66,7%) 17q12DS individuals showed renal abnormalities later in infancy, puberty, or early adult life. Regardless of the initial clinical indication for testing, identification of 17q12 deletions should always be accompanied by regular blood and urine tests and sonographic kidney evaluation.

The frequency of diabetes in individuals with *HNF1B*-related clinical phenotypes is highly variable, ranging from 9% to 82% with a mean age of diagnosis at 24 years, but neonatal onset is also possible (Table 2).^{9,12,48,49} Consistently, two 17q12DS individuals (I5 and I6) were diagnosed with diabetes in puberty, whereas individual I1 showed slightly increased levels of blood glucose in early infancy, which could be considered as a first indication of the presence of diabetes. Further subsequent glucose measurements at a later age were though not available. The remaining individuals did not exhibit diabetes to date, yet at least for individuals I2 to I4, this may relate to their young age. The severity of diabetes was shown to be similar in both carriers of truncating and missense variants. Dubois-Laforgue et al reported a lower body mass index (BMI) and more severe diabetes observed at diagnosis in 17q12DS as compared with intragenic variant cases.⁹ In addition to annual glycated hemoglobin (HbA1c) and glucose level measurements, both carriers of 17q12DS and intragenic *HNF1B* variants should be trained to self-monitor diabetes symptoms in order to enable early diagnosis and avoid complications.

Other noteworthy clinical features of the herein described individuals are short stature in individual I4, uterus aplasia in individual I7, and strabism in individuals I4, I5, and I7. Gonadotrophin treatment increased the predicted final adult height of individual I4 for about 10 cm. Yet reports on growth restriction in individuals with 17q12DS²⁹ or *HNF1B* intragenic variants³⁶ are rare, and the efficacy of growth hormone treatment in these cases needs elucidation. Uterus aplasia is within the *HNF1B*-associated spectrum, with intragenic variants and whole deletions reported in 18% to 50% of women with uterine and renal anomalies.^{9,24} Thus, obstetric evaluation already at young age is required. Finally, detailed ophthalmic examination is warranted, since in 40% to 44% of *HNF1B* aberration carriers, strabism and other ocular anomalies were reported (Table 2).¹⁰

The reasons for the phenotypic variability within the two groups of individuals with *HNF1B* intragenic alterations and whole deletions, as well as between these groups, currently remain unclear. The clinical diversity observed within the 17q12DS carriers could be attributed to the incomplete penetrance and variable expressivity of this CNV, similar to other recurrent microdeletions.⁵⁰ A variable quantitative impact of the 17q12 microdeletion, which is difficult to be ascertained from the small cohorts examined, could, for instance, justify the presence or absence of NDDs in affected individuals.^{50,51} Regarding clinical differences within the intragenic variants group, different

pathomechanisms, especially for the missense variants, constitute a possible hypothesis. Indeed, a dominant negative effect, allowing a residual function of the *HNF1B* protein rather than haploinsufficiency, has been discussed for some variants.⁵² The differential phenotypic presentation between the 17q12DS and intragenic aberration cohorts could be explained by the concurrent loss of other genes encompassed in the microdeletion and interruption of interaction cascades with transcription factors or other regulatory elements. For instance, haploinsufficiency of two other genes (*ACACA*, MIM *200350; and *ZNHIT3*, MIM *604500) was indicated as the cause of the leaner figure and more severe diabetes at onset in 17q12DS cases.⁹ This hypothesis was also suspected for the presence of NDDs in individuals with microdeletions.^{33,43} From the remaining 37 protein-coding genes encompassed in the deletion, seven have been implicated with NDDs, of which only *PCGF2* (MIM *600346) with dominant⁵³ and *PIGW* (MIM *610275) with recessive inheritance⁵⁴ have a confirmed association, whereas the rest are considered candidate genes. Consequently, *PCGF2* is the most notable candidate; however, it does not seem to be intolerant to heterozygous loss-of-function and missense variants (pLI = 0.85, Z score = 1.21), and all described *PCGF2* carriers have the same recurrent missense variant with dominant negative effect (Supplementary File 1).⁵³ In agreement, in the largest study attempting a genotype/phenotype correlation in 75 individuals with *HNF1B* alterations, no clear phenotypic differences regarding renal disease were identified between 17q12DS and intragenic variant carriers.¹¹ Therefore, the possibility remains that *HNF1B* is indeed the critical gene for all associated phenotypes and that most of the variability is caused by additionally modifying genetic and developmental factors.

To date, only one recent study applying exome sequencing for CAKUT cases prenatally detected a *HNF1B* frameshift variant.⁵⁵ Likewise, the herein reported prenatal identification of an intragenic *HNF1B* variant in individual I1 is likely a consequence of increased availability and demand for such NGS-based techniques. Because of the known high frequency of intragenic *HNF1B* variants in fetal autopsy cases^{8,19,27,56} or in postnatally diagnosed children with renal diseases,^{11,15,22,30,34,36} *HNF1B* mutation screening should be an integral part of prenatal diagnosis for hyperechogenic/multicystic kidneys. Customized targeted panels capturing multiple cystic kidney disease-related genes, like the one used herein, have several favorable features for the prenatal setting: high coverage, short turnaround times, and compatibility with small benchtop sequencing machines. Clinical exome sequencing (covers approximately 5000 to 7000 disease genes) is currently a reasonable compromise, although it requires more time and is less accessible. Regardless, NGS should be recommended concurrently with CMA for rapid prenatal diagnosis in fetuses with hyperechogenic or cystic kidneys. However, the application of next-generation methods will consequently result in the increased identification of pathogenic variants and variants of unknown significance (VUS). To facilitate fast and effective assessments, all identified variants should be systematically classified and deposited in appropriate databases, as performed in this study for all

described in the literature so far (Supplementary Note and Supplementary File 1).

In conclusion, similar to previous studies, our study indicated no differences in the prenatal renal phenotypic spectrum between intragenic *HNF1B* aberrations and 17q12DS, and a wide range of postnatal renal and extra-renal abnormalities for both. The most prominent postnatal phenotypic differences, potentially affecting prenatal decision making, are a more severe progress of renal impairment in individuals with intragenic *HNF1B* variants and the increased NDD risk, which is a confirmed feature in 17q12DS and suspected in *HNF1B* intragenic variant carriers. Incomplete references to the overall clinical presentation of the affected individuals in the published reports and previous classifications of identified variants not following current recommendations of a standardized five-tier system add to the difficulty of risk estimation. We, therefore, systematically collected *HNF1B*-related clinical traits, revised and harmonized all intragenic variants from 88 articles, and proposed a minimal reporting scheme for *HNF1B*-associated disease (Table 2). Building on these efforts, future studies using a standardized ascertainment of phenotype/genotype information will improve our understanding and characterization of *HNF1B*-associated disorders and enable the optimization of genetic counseling.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

B.P. and G.V. conceived the study. B.P., J.H., C.T.T., J.S., M.Za., M.S., F.F., and C.Z. provided patients' data and performed clinical assessments. B.P., M.K., C.K., S.U., A.B.E., and A.Re. analyzed and interpreted the molecular data. M.Zw. and A.Ra. designed and provided the custom panel. B.P. created the figures and supplementary files. B.P. and G.V. performed the variant review and standardization. G.V. and C.Z. retrospectively collected patient data and wrote the case reports. G.V., C.Z., and B.P. wrote and edited the manuscript. J.H., C.T.T., J.S., M.Za., M.K., C.K., M.Zw. S.U., A.B.E., M.W.B., M.W., A. Ra. F.F., and A.Re. reviewed the draft manuscript.

ETHICS APPROVAL

Informed written consent was obtained from all patients or their legal guardians, and the study was approved by the Ethical Review Board of the Friedrich-Alexander-Universität Erlangen-Nürnberg.

DATA AVAILABILITY STATEMENT

The data supporting this article are provided in the supplementary files available from the publisher's website.

Web links:

CADD: <https://cadd.gs.washington.edu/score/>

gnomAD: <http://gnomad.broadinstitute.org/>

MutationTaster: <http://www.mutationtaster.org/>

SnEff/SnpSift: <http://snpeff.sourceforge.net/>

DECIPHER: <https://decipher.sanger.ac.uk/>

dbNSFP: <https://sites.google.com/site/jpopgen/dbNSFP/>

Genomics England PanelApp: <https://panelapp.genomicsengland.co.uk/>

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SUPPORTING INFORMATION

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